HEALTH RISK ASSESSMENT: DOMESTIC AUTOMATIC INSECTICIDE DISPENSERS

NOVEMBER 2015

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CLIENT REPORT No:	**FW15050**
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EXECUTIVE SUMMARY

Insecticidal formulations used in automatic insecticide dispensers usually contain two main components of toxicological concern; an insecticidal agent and a synergist. Synergists inhibit the mixed function oxidase enzymes that detoxify the insecticidal agent. The insecticidal agents used in automatic insecticide dispensers in New Zealand are pyrethrins and/or synthetic pyrethroids. The pyrethroids used are mainly Type I or older Type II pyrethroids and are mostly of low toxicity. The synergists used are either piperonyl butoxide (PBO) or N-octyl bicycloheptene dicarboximide (MGK 264).

There is good evidence for acute adverse health effects in humans associated with exposure to the insecticidal chemicals present in automatic insecticide dispensers (pyrethrins/pyrethroids), but limited evidence of adverse health effects from operation of automatic insecticide dispensers, or from chronic low dose exposures. There is little evidence of adverse health effects in humans from exposure to synergists. However, humans will rarely be exposed to these chemicals in isolation from insecticidal agents.

New Zealand incident surveillance (calls to National Poisons Centre) identified only one incident of human exposure to the contents of automated insecticide dispensers. No hospitalisations or deaths from use of these products in New Zealand were recorded in data held by the Centre for Public Health Research.

Due to the diversity of insecticidal active ingredients used in these products, risk assessment of pyrethrins/pyrethroids was carried out using a cumulative risk assessment approach, as these insecticides are considered to exert their toxicity by a common mode of action, specifically interaction with voltage-gated sodium channels in nerve tissues. Relative potency factors were available for all relevant insecticides, except transfluthrin. It was assumed that the potency of transfluthrin was equivalent to that of the reference pyrethroid (deltamethrin). There is no evidence that the synergists used in these products can be considered as a common mechanism group and this assessment has considered exposure to automatic insecticide dispenser formulation in terms of three separate components; pyrethrins/pyrethroids as deltamethrin equivalents, PBO and MGK 264.

Exposures were considered in terms of a realistic worst-case scenario; installation of the automatic insecticide dispenser in the bedroom of an infant (<1 year). The dispenser was assumed to operate 24 hours per day. Daily exposure was assessed as the aggregate of: inhalation during eight hours of sleeping, dermal exposure during eight hours of sleeping (assuming exposure of the head only) and during one hour of crawling (contact with insecticide formulation deposited on the floor) and oral exposure due to non-respirable particles being ingested during sleep and deposition of insecticide formulation on food. It was assumed that only one meal per day would be affected and that deposition on food was the same as deposition on the floor of the bedroom. Adult exposure potentially associated with insecticide formulation reservoir installation was also considered, assuming an accidental two second activation of the dispenser. Exposures were aggregated over all identified exposure routes. Absorption of all compounds was assumed to be 100% following inhalation or oral exposure and 10% following dermal exposure.

Risks associated with aggregate pyrethrin/pyrethroid cumulative exposures were assessed by margin of exposure (MoE), while aggregate exposures for PBO and MGK 264 were assessed against acute and chronic population adjusted doses (PADs).

Infant pyrethrin/pyrethroid aggregate cumulative exposure were at a MoE of 224, less than the target MoE of 300, proposed by USEPA for this age group. Acute aggregate exposures

to PBO and MGK 264 were less than the respective aPADs. However, chronic aggregate exposures to PBO and MGK 264 approached or exceeded respective cPADs.

While most assumptions made in this exposure assessment will tend to overestimate exposure to components of automatic insecticide dispenser formulation, these results suggest that use of such dispensers under the conditions of this scenario may lead to undesirably high exposure to the component chemicals. The two largest components of the aggregate exposure estimates are from inhalation during sleep and consumption of contaminated food. This suggests that these dispensers are probably best installed in well-ventilated living spaces, rather than in bedrooms or food preparation areas.

Adult exposures to automatic insecticide dispenser formulation during reservoir installation is unlikely to result in acute adverse health effects.

GLOSSARY

Acute toxicity	1. *Adverse effects* of finite duration occurring within a short time (up to 14 days) after administration of a single *dose* (or *exposure* to a given *concentration*) of a test substance or after multiple doses (exposures), usually within 24 hours of a starting point (which may be exposure to the *toxicant*, or loss of reserve capacity, or developmental change, etc.) 2. Ability of a substance to cause *adverse effects* within a short time of dosing or *exposure*
Adverse effect	A change in biochemistry, physiology, growth, development morphology, behaviour, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to other environmental influences
Benchmark response (BMR)	A specified change in biological response compared to background. For example, a 10% increase in the number of animals developing fatty liver compared with untreated animals
Dermal	Cutaneous, pertaining to the skin
Dose	Total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue
Dose response	Association between dose and the incidence of a defined biological effect in an exposed population
Dose response assessment	Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose–response assessment is the second of four steps in risk assessment
Exposure assessment	Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment
Harm	An adverse effect. Damage or adverse effect to a population, species, individual organism, organ, tissue, or cell
Hazard identification	The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment
Incidence	Number of occurrences of illness commencing, injury, or of persons falling ill, during a given period in a specific population usually expressed as a rate
Injury	Any physical harm or damage serious enough to warrant medical treatment by a health professional either at the scene or in a hospital or primary care practice

Margin of exposure (MOE)	Ratio between a defined point on the dose-response curve (eg. NOAEL) for the adverse effect and the estimated human exposure
No observed adverse effects level (NOAEL)	Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure
Ocular	Pertaining to or via the eyes
Oral	Pertaining to or via the mouth
Permanent harm	An adverse effect from which the subject does not recover
Point of departure	A dose level used to quantify risk
Risk characterisation	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. Risk characterisation is the fourth step in the risk assessment process
Toxicological endpoints	An observable or measurable biological event or chemical concentration (e.g. metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure

1. INTRODUCTION

The purpose of this report is to develop a generic health risk assessment for domestic automatic insecticide dispensers. This report will only consider domestic, non-occupational, routine and incidental exposure to insecticide ingredients from operation of automatic insecticide dispensers. Exposure scenarios will be developed for the most common or likely exposure events.

1.1 CONSUMER PRODUCTS DESCRIPTION – AUTOMATIC INSECTICIDE DISPENSERS

Automatic insecticide dispensers are similar to conventional 'fly sprays', except the insecticide reservoir is encased in a battery operated unit that emits a metered quantity of aerosolised insecticide at defined intervals (usually about 5 to 30 minutes). While these dispensers are primarily for the control of flying insects, they also offer control of crawling insects.

1.2 PREVALENCE OF USE

No data were found on the prevalence of domestic automatic insecticide dispensers in New Zealand or internationally. The harmonised system (HS), used to describe goods in international trade, including those imported into New Zealand, does not allow identification of import quantities of insecticide dispenser units or the relevant insecticides.

1.3 INSECTICIDE ACTIVE INGREDIENTS IN SPRAY FORMULATION

The insecticide reservoirs are sold in a pre-packaged form, with a mixture of dispenser-specific products and generics. The active ingredients are often pyrethrins, natural insecticides extracted from flowers of chrysanthemum species, and piperonyl butoxide, a synergist that inhibits enzymes that break down pyrethrins. Alternatively, the active insecticide may be a mixture of pyrethroids, synthetic analogues of the pyrethrins, such as permethrin and allethrin. When synthetic pyrethroids are used, the formulation may contain a mixture of pyrethroids or a mixture of pyrethroids and pyrethrins.

Table 1 summarises compositional information of sprays used in automatic insecticide dispensers in New Zealand.

Table 1. Composition of spray formulations used in automatic insecticide dispensers in New Zealand

Brand	Manufacturer	Composition	Reference
Ecomist	Damar Industries	Pyrethrins (9 g/kg), piperonyl butoxide (45 g/kg)	http://www.ecomist.co.nz/content/Insect-Control/29.aspx
Expra	STM Group (NZ)	Pyrethrins (9 g/kg), piperonyl butoxide (45 g/kg) D-allethrin (4.4 g/kg), tetramethrin (3.5 g/kg), pyrethrins (1.1 g/kg), piperonyl butoxide (45 g/kg) Tetramethrin (4.6 g/kg), D-phenothrin[a] (0.83 g/kg), permethrin (1.6 g/kg)	http://expra.stmgroup.co.nz/index.php
Mortein	Reckitt Benckiser	Transfluthrin (6.0 g/kg), permethrin (8.0 g/kg) Pyrethrins (9.75 g/kg), piperonyl butoxide (15.6 g/kg), n-octyl	http://www.mortein.co.nz/pest-control-products.php

Brand	Manufacturer	Composition	Reference
		bicycloheptene dicarboximide (29.89 g/kg)	
Pestrol	Pestrol	Pyrethrins (9.25 g/kg)	http://www.pestrol.co.nz/
Py-Zapp	Pest It Pty	Pyrethrins (9 g/kg), piperonyl butoxide (42.3 g/kg)	http://www.pestit.com/files/py-zapp.html
Raid	SC Johnson and Son	Pyrethrins (9 g/kg), piperonyl butoxide (45 g/kg), or Allethrin 20:80 (4.4 g/kg), tetramethrin (3.5 g/kg), pyrethrins (1.1 g/kg), piperonyl butoxide (45 g/kg)	http://www.raidautomatic.com.au/index.html

[a] D-phenothrin is also known as sumithrin

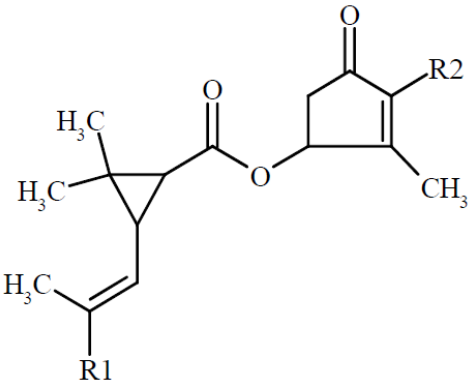
Table 1 lists the active ingredients in the various spray formulations. The balance of the contents of the spray reservoirs is hydrocarbon propellants (propane or butane).

1.3.1 Description of the active ingredients

Pyrethrins

Pyrethrins (pyrethrum extract) are a group of six structurally-related insecticidal esters extracted from flowers of chrysanthemum species, most commonly *Chrysanthemum cinerariaefolium* (Ministry of Health (Italy) 2008). The esters are grouped into Pyrethrin I (pyrethrin 1, cinerin 1 and jasmolin 1) and Pyrethrin II (pyrethrin 2, cinerin 2 and jasmolin 2). The structures of the esters are shown in Figure 1.

Figure 1. Chemical structure of the insecticidal esters present in pyrethrins



Pyrethrin I: R1 = CH_3; R2 = $CH_2CH{=}CHCH{=}CH_2$
Pyrethrin II: R1 = $COOCH_3$; R2 = $CH_2CH{=}CHCH{=}CH_2$
Cinerin I: R1 = CH_3; R2 = $CH_2CH{=}CH_3$
Cinerin II: R1 = $COOCH_3$; R2 = $CH_2CH{=}CH_3$
Jasmolin I: R1 = CH_3; R2 = $CH_2CH{=}CHCHCH_3$
Jasmolin II: R1 = $COOCH_3$; R2 = $CH_2CH{=}CHCHCH_3$

Reproduced from (USEPA 2006c)

Refined pyrethrum extract contains 45-55% pyrethrins, 23-25% other phytochemicals, including triglyceride oils, terpenoids and carotenoid plant pigments, 20-25% light isoparaffins and 3-5% butylated hydroxytoluene (BHT) (JMPR 1999). BHT is added during or after processing, to prevent oxidation.

Pyrethrins exert their insecticidal toxicity by altering nerve function through modification of the normal biochemistry and physiology of nerve membrane sodium channels (USEPA 2006c).

Synthetic pyrethroids

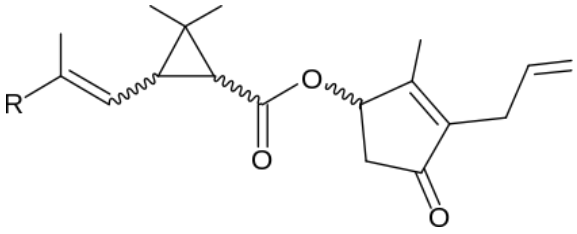
Synthetic pyrethroids have insecticidal properties similar to pyrethrins, but have greater stability to light and heat. Pyrethroids can be structurally divided either on the basis of age or the presence of an α-cyano group (USEPA 2011a). Older pyrethroids were based on chrysanthemic acid and characterised by a cyclopropane ring, bonded to a carboxylic acid

moiety and a variety of halogenated and non-halogenated substituents. More recent pyrethroids do not have the cyclopropane ring structure. Pyrethroids without a α-cyano group are usually referred to as Type I pyrethroids, while those with the α-cyano group are referred to as Type II pyrethroids. Figure 2 shows examples of the various groups. Allethrin is one of the oldest synthetic pyrethroids and is a Type I pyrethroid, cypermethrin is an older Type II pyrethroid, and fenvalerate is a more recent Type II pyrethroid. The α-cyano group enhances the toxicity of pyrethroids carrying this substituent.

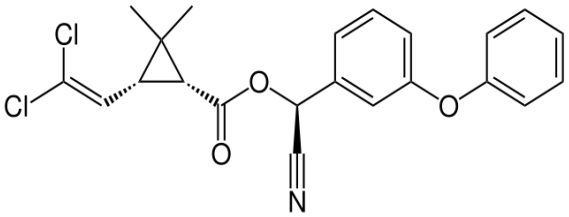
USEPA considered the modes of action of the various pyrethroids and pyrethrins and concluded that they all share a common mode of action; interaction with voltage-gated sodium channels (VGSCs) in nerve tissues (USEPA 2011a). Pyrethroids delay the inactivation of affected VGSCs, allowing for an increase in sodium ion influx and resulting in delayed repolarisation. The delay is greater due to Type II pyrethroids (>>200 ms) than for the Type I pyrethroids (~20ms). Mixed-Type pyrethroids (e.g. esfenvalerate and fenpropathrin) produce delays intermediate between the Type I and Type II pyrethroids.

Figure 2. Examples of structural types of pyrethroids

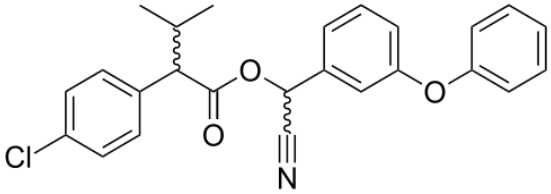
Allethrin (Type I)



Cypermethrin (older Type II)



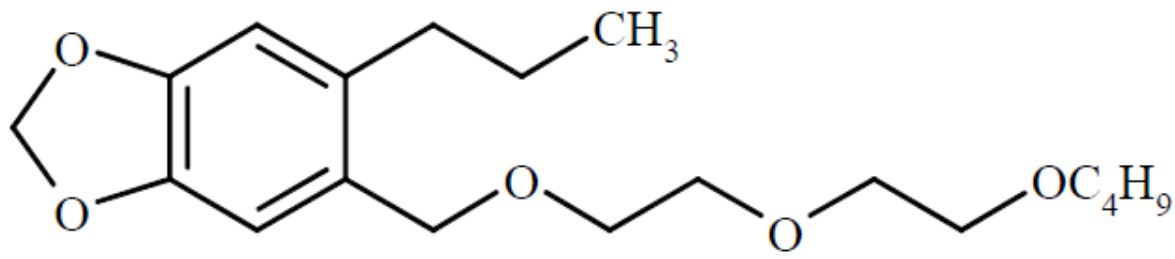
Fenvalerate, (newer Type II)



Piperonyl butoxide

Piperonyl butoxide (PBO) is included in insecticide preparations as a synergist, inhibiting detoxification of an associated pesticide by insect pests (USEPA 2006b). PBO inhibits microsomal enzymes, specifically the mixed function oxidase (MFO) system, by directly binding to the enzymes. The structure of PBO is shown in Figure 3.

Figure 3. Chemical structure of piperonyl butoxide (PBO)



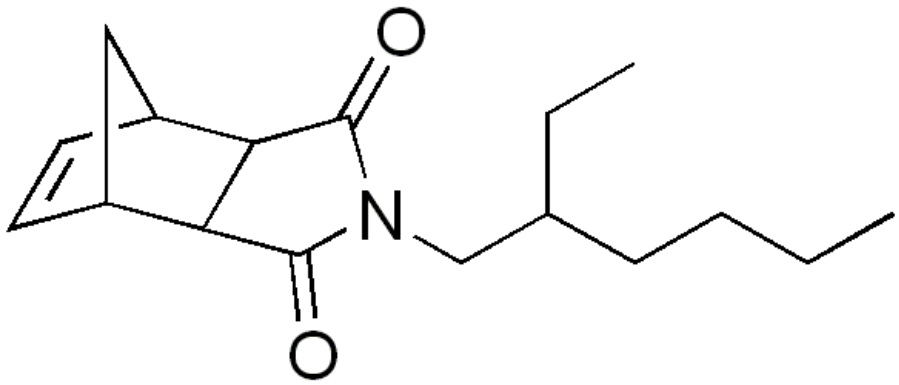
Reproduced from (USEPA 2006b)

Humans also have an MFO system. However, evidence suggests that inhibition of MFO enzymes in mammals by PBO is transient and only occurs at high PBO doses (JMPR 1996).

N-octyl bicycloheptene dicarboximide (MGK 264)

N-octyl bicycloheptene dicarboximide, also known as MGK 264, is sometimes used as an alternative synergist to PBO (JMPR 1967). MGK-264 inhibits microsomal enzymes in insects by binding directly to these enzymes and thereby inhibiting the breakdown of other pesticides such as pyrethrins and pyrethroids. The structure of MGK 264 is shown in Figure 4.

Figure 4. Chemical structure of MGK 264



Reproduced from https://en.wikipedia.org/wiki/N-Octyl_bicycloheptene_dicarboximide#/media/File:MGK-264.png

1.4 REGULATORY SITUATION IN NEW ZEALAND

Aerosol spray products, used as insecticide reservoirs in automatic dispensers are regulated under the Hazardous Substances New Organisms Act 1996. Inspection of products for sale through local supermarkets found that the most commonly available products identified have approval under the Group Standard for flammable aerosols (HSR002515).[1]

1.5 INCIDENT SURVEILLANCE IN NEW ZEALAND

During the period 2008 to 2012, there was one call to the National Poisons Centre (NPC) related to automatic insecticide dispensers (Helene Marsters, Centre for Public Health Research, personal communication). The incident involved ingestion of liquid contents by an

[1] http://www.epa.govt.nz/Publications/gs-aerosols-flammable.pdf Accessed 27 August 2015

adult female. During the same period, the NPC received a total of 132 insecticide-related calls.

No hospitalisations or deaths associated with automated insecticide dispensers were identified.

2. HAZARD IDENTIFICATION

2.1 HEALTH EFFECTS – AUTOMATICALLY DISPENSED INSECTICIDE

2.1.1 Regulatory assessments

No regulatory assessments specific to automatic insecticide dispenser formulations were found.

2.1.2 Observations in humans

In May 1999, three cases of pesticide-related illness were reported to the Florida Department of Health associated with improperly placed automatic insecticide dispensers (Shafey et al 2000). The active ingredients released by the dispensers were pyrethrin and PBO. The circumstances and symptoms were:

- A 42-year-old cook developed a sore throat, dyspnea (shortness of breath), headache and dizziness after several hours exposure to mists from the insecticide dispenser in the food preparation area. The cook removed the dispensers and noted relief of symptoms.
- A 40-year-old male customer developed headache and dyspnea within one hour of entering the restaurant. Symptoms lasted approximately four hours.
- A 47-year-old male customer experienced a burning sensation in his left eye swelling, redness and irritation of the eyelid. Symptoms persisted for about 24 hours. An insecticide dispenser was located about two metres from the table the customer occupied and was facing his left eye.

In a separate incident, in August 1995, a 17-year-old male restaurant employee received a direct dose of insecticide to his right eye while changing the dispenser cartridge (Shafey et al 2000). He experienced an immediate burning sensation in the eye and sought medical assistance.

Review of national and state poisoning surveillance systems in the United States identified 94 pyrethrin-PBO exposed cases associated with automatic insecticide dispensers during the period 1986 to 1999 (Shafey et al 2000). The majority of cases (*n* = 55, 59%) were work-related, with seven cases identifying that the exposure occurred while insecticide cartridges were being changed. Signs and symptoms most commonly involved the eye (*n* = 36, 38%), the neurological systems (*n* = 26, 28%), the respiratory system (*n* = 23, 24%) and the gastrointestinal system (*n* = 20, 21%).

2.2 HEALTH EFFECTS – PYRETHRIN/PIPERONYL BUTOXIDE INSECTICIDES

2.2.1 Regulatory assessments

Regulatory assessments of these compounds have been performed individually, but not for the combination of active ingredients.

2.2.2 Observations in humans

Monitoring of poisonings in the human population will sometimes identify pyrethrin-PBO insecticides, without identifying specifics of the exposure circumstances.

The American Association of Poison Control Centers (AAPCC) supports the United States network of 56 poison centres.[2] The association publishes an annual report including summary statistics of all exposures reported to the poison centres during a calendar year. Table 2 summarises the data for pyrethrin-PBO insecticides for the period 2000-2011. While reports are available for the 2012 and 2013 years, no cases of pyrethrin-PBO poisoning were reported in these years. Through the entire period there were separate categories for 'pyrethrin' and 'pyrethrins'. It is uncertain whether these categories contain poisonings due to pyrethrin-PBO formulation. It seems clear that the emergence of the synthetic pyrethroids, from no cases in 2000 to more than 20,000 cases from 2006 onwards (see Table 3) is, at least partially, responsible for the decline in poisonings due to pyrethrin-PBO formulations.

No deaths were reported due to pyrethrin-PBO poisoning and few major consequences.

An analysis of data on calls to US poison centres for the years 2001-2003 identified 15,427 calls related to pyrethrins and/or PBO (Osimitz et al 2009). Moderate medical outcomes were reported in 614 (4.0%) incidents, while major outcomes were reported in 19 (0.1%) incidents. Exposures involved a disproportionate number of children less than six year (35% of calls, while this groups constitutes only 10% of the population). Most exposures occurred at the callers own residence (94%), were managed on-site (81%) and were unintentional (94%). Exposures were predominantly through ingestion (34.2%), followed by inhalation (27.6%), dermal contact (27.2%) and ocular contact (10.0%). Major outcomes were more common following inhalation exposure.

[2] http://www.aapcc.org/ Accessed 21 August 2015

Table 2. Incidents of pyrethrin-piperonyl butoxide poisoning reported to US poison centres 2000-2011

Year[1]	Exposures reported		Age (years)					Reason				Treated in healthcare facility	Outcome[3]				
	Total	PPB	<6	6-12	13-19	>19	Unkn	Unint	Int	Other	Adv Rxn		None	Minor	Mod	Major	Death
2000	2168248	6379	2337		814	3160		5945	180	52	198	1208	1038	1304	382	9	0
2001	2267979	3642	1348		536	1723		3362	101	21	155	664	590	796	159	8	0
2002	2380038	1123	417		140	560		1055	34	5	29	183	154	202	47	1	0
2003	2395582	339	155		52	129		324	6	2	6	57	56	75	18	0	0
2004	2438644	321	110		33	175		290	7	0	23	74	30	103	22	0	0
2005	2424180	309	93		48	165		285	11	1	12	81	35	85	19	1	0
2006[2]	2403539	311	97		45	113		254	7	2	18	62	35	67	15	0	0
2007	2482041	290	90		54	118		261	6	2	10	56	39	69	9	1	0
2008	2491049	305	124		40	107		272	3	0	10	44	49	53	13	0	0
2009	2479355	246	98	30	14	72	15	211	7	0	9	46	37	43	16	0	0
2010	2384825	173	66	21	6	51	14	147	3	0	8	24	19	37	8	0	0
2011	2334004	4	1	1	1	1	0	2	0	0	2	3	1	0	1	0	0

PPB = pyrethrin-piperonyl butoxide insecticides

Unkn = unknown

Unint = unintentional exposures, including passive environmental exposure, occupational exposure, therapeutic error or unintentional misuse

Int = intentional exposures, including suspected suicide and improper or incorrect use of a substance for a purpose other than its intended purpose

Adv Rxn = adverse reaction, an adverse event occurring with normal, prescribed, labelled, or recommended use of the product, as opposed to overdose, misuse, or abuse, including allergic, hypersensitive and idiosyncratic reactions

Mod = moderate

[1] Report references: (Bronstein et al 2007; Bronstein et al 2008; Bronstein et al 2009; 2010; Bronstein et al 2011; Bronstein et al 2012; Lai et al 2006; Litovitz et al 2001; Litovitz et al 2002; Watson et al 2003; Watson et al 2004; Watson et al 2005)

[2] From 2006 onwards there was a change in the way demographic information was reported; the 'PPB' exposure count represents all recorded exposures, but the counts in subsequent columns report single substance exposures only. Over all exposures, single substance exposures account for just over 90% of all exposures

[3] Minor = The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes.

Moderate = The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement

Major = The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement

2.3 HEALTH EFFECTS – PYRETHRINS

2.3.1 Regulatory assessments

Pyrethrins have been assessed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), the European Food Safety Authority (EFSA) and the United States Environmental Protection Agency (USEPA).

JMPR

JMPR assessed pyrethrins in 1965, 1966, 1967, 1968, 1969, 1970, 1972, 1999 and 2003. The following conclusions come from the two most recent assessments (JMPR 1999; 2004):

- Pyrethrins show little acute toxicity, with oral LD_{50} (rat) >1200 mg/kg, dermal LD_{50} (rabbit) >2000 mg/kg and inhalation LC_{50} (rat) of 3.4 mg/L. The compounds show minimal ocular and dermal irritation and no potential for skin sensitisation.
- The liver is the main target organ in rats, mice and dogs with effects including increased liver weight, changes in enzyme activities (transaminase and microsomal enzymes), hepatocellular hypertrophy and anaemia.
- Long-term studies on rats showed an increased incidence of benign tumours of the skin, liver and thyroid. However, these effects were considered to be threshold effects, with negligible relevance to human exposure levels.
- Pyrethrins are not mutagenic or genotoxic.
- Pyrethrins do not show developmental toxicity (rat, rabbit), but reduced body weights were observed in offspring (rat) at parentally toxic doses.
- Acute neurotoxicity (tremors, wetness of urogenital region, salivation, perinasal encrustation, exaggerated startle response, decreased grip strength, hind-leg play) and behavioural effects (increased motor activity, decreased rearing and ambulation) were observed with a NOAEL of 20 mg/kg bw.
- Available human data did not show a causal relationship between pyrethrin exposure and significant adverse health effects. There was no evidence that a history of asthma was disproportionately associated with major adverse outcomes.

JMPR established an acceptable daily intake (ADI) of 0-0.04 mg/kg bw, based on a NOAEL of 4 mg/kg bw/day in a long-term rat study and a safety factor of 100. Acute toxicity was considered to be different to chronic toxicity and an acute reference dose (ARfD) of 0.2 mg/kg bw was established, based on the NOAEL for acute neurotoxicity in rats and a safety factor of 100.

EFSA

The European assessment process involves preparation of an assessment dossier by a member country, followed by peer review of the assessment by EFSA (EFSA 2013). The assessment of pyrethrins was carried out by Italy (Ministry of Health (Italy) 2008). A public version of the assessment dossier is available on request.

With respect to mammalian toxicity, the assessment conducted by Italy did not reach any markedly different conclusions to those reached by JMPR. The assessment proposed an ADI of 0.04 mg/kg bw, but did not propose an ARfD.

In their peer review of the assessment EFSA noted that:

- No conclusions could be drawn on the toxicological relevance of impurities in the pyrethrum extract and whether the batches used in the toxicological studies were representative of the technical specification.
- Due to local effects by inhalation at low doses in rats (squamous metaplasia), and indications of local genotoxicity in an *in vitro* Comet assay with human nasal mucosal cells, without evidence of a threshold, the risk assessment for operators, workers and bystanders could not be concluded.
- Toxicological assessment of the hydroxylated chrysanthemic acid plant metabolites was not included.

EFSA noted that "Based on the standard battery of genotoxicity studies, pyrethrins are considered unlikely to be genotoxic" (EFSA 2013). However, the fact that the Comet assay was conducted with human nasal mucosal cells raises the possibility of a localised genotoxic effect of particular relevance to inhalation exposure.

The local effect seen in the rodent larynx following inhalation exposure to pyrethrins (squamous metaplasia) has been the subject of a critical review (Osimitz et al 2007). The review concluded that these effects could be induced by a wide range of chemically dissimilar substances and should be viewed as an adaptive response, rather than as a precursor to neoplastic changes.

USEPA

The findings of the full USEPA risk assessment for pyrethrins were included in the reregistration eligibility decision (RED) for pyrethrins (USEPA 2006c). USEPA's toxicological evaluation reached similar conclusions to the JMPR and EFSA assessments, with neurobehavioural effects judged to be the key acute effect and effects on the liver and thyroid judged to be the key chronic effects.

USEPA used the same NOAELs as JMPR to derive health-based exposure limits for acute (acute population adjusted dose; aPAD) and chronic (chronic population adjusted dose; cPAD) exposure. For acute exposures, USEPA applied an additional three-fold safety factor due to database uncertainties. This was due to the fact that the database did not include a developmental neurotoxicity study. The resulting aPAD was 0.07 mg/kg bw/day, while the cPAD was 0.044 mg/kg bw/day.

2.3.2 Observations in humans

Although reported exposure to pyrethrins may actually be exposure to a pyrethrin-PBO formulation, the current report has separated instances where PBO is not specifically mentioned.

A five-year review of pyrethrin and pyrethroid illnesses in Washington and Oregon states (US) identified 172 cases out of 534 (32%) as due to exposure to pyrethrins (Walters et al 2009). The severity of illness due to pyrethrin exposure was low in 163 cases (95%), with only one case classified as high severity. The severe case involved co-application of a pyrethrin-PBO formulation with a synthetic pyrethroid (esfenvalerate) by a licensed pesticide applicator. An elderly woman, with a history of heart disease, in the house experienced acute respiratory symptoms and cardiac arrhythmia and subsequently died. The woman's husband, two neighbours and five responders experienced less severe upper respiratory tract symptoms, which resolved within several hours of leaving the house.

A US analysis of acute pesticide poisonings in the retail sector (1998-2004) identified 22 low severity and 3 moderate severity cases[3] due to pyrethrin exposure (Calvert et al 2007). A fatality was identified, where exposure was to a rodenticide and a pyrethrin-PBO formulation. The exposure exacerbated existing asthma and, after approximately one month, the steroid treatment of the asthma complication resulted in a bleeding duodenal ulcer, leading to gastrointestinal haemorrhage and death.

An updated US analysis of acute illness due to pyrethrin/pyrethroid exposure, covering the period 2000 to 2008, identified 547 cases associated with pyrethrin exposure (Hudson et al 2014). Of these cases, 445 (81%) were identified as of low severity and 102 (19%) of moderate or high severity. Respiratory symptoms were reported in 44% of pyrethrin exposures, while dermal symptoms were reported in 26% of cases. Cough (*n* = 124) and dyspnea (*n* = 101) were the main respiratory symptoms associated with pyrethrin exposure. Other common symptoms included eye pain/irritation (*n* = 179), headache (*n* = 130) and nausea (*n* = 128). No further fatalities due to pyrethrin exposure were identified, other than the two summarised above.

Evaluations of pyrethrins by the JMPR noted that the adverse effects reported following human exposure to pyrethrins were effects on the skin and respiratory tract (JMPR 1999). It was reported that a sesquiterpene lactone, pyrethrosin, had been isolated from pyrethrins and was able induce dermal reponses in humans.

A more recent JMPR evaluation summarised the results of a study to analyse incidents of exposure to products containing pyrethrins during the period 1994 to 1999, conducted by the American Association of Poison Control Centers (AAPCC) (JMPR 2004). The study concluded that:

- Adults accounted for 45% of exposures, while young children (<5 years) accounted for 37% of exposures.
- One-third of exposures were through ingestion, while inhalation, dermal and ocular exposures accounted for 27.8%, 26.2% and 10.7% of exposures, respectively.
- Where medical outcome was known, 30.5% of cases were asymptomatic and symptoms in 22.4% of cases were considered to be unrelated to the exposure. Minor, moderate or major symptoms were reported for 38.9%, 7.8% and 0.2% of cases, respectively. No deaths were reported.
- Exposure of children was more likely to be associated with ocular or dermal exposure.
- Major outcomes were more frequently associated with respiratory or neurological symptoms.

An Italian case report describes nasal irritation followed by gradual anosmia (absence or diminution of olfactory function) following extended exposure (several days, six hours per day) to a pyrethrin-treated environment (Gobba and Abbacchini 2012). At the time of reporting, the anosmia had persisted for more than two years and appeared likely to be permanent.

[3] Cases were classified as low severity if three or fewer days of work were missed and the health effects were not likely to require treatment. Moderate severity related to health effects that are not life-threatening, but required medical treatment and resulted in time lost from work (usually less than 5 days). High severity refers to health effects that are life-threatening and require hospitalisation and usually more than 5 days off work.

2.4 HEALTH EFFECTS – SYNTHETIC PYRETHROIDS

2.4.1 Regulatory assessments

Due to the large number of synthetic pyrethroids that have been developed a correspondingly large number of regulatory assessments have been carried out. However, the current assessment will restrict itself to synthetic pyrethroids used in automatic insecticide dispenser formulations in New Zealand; D-allethrin, tetramethrin, D-phenothrin, transfluthrin and permethrin (see Table 1). All but one of these pyrethroids (tetramethrin) are Type I pyrethroids, which have a lesser impact on the VGSCs than Type II pyrethroids (USEPA 2011a). Tetramethrin is an older Type II pyrethroid.

While earlier regulatory assessments considered pyrethroids compound by compound, the USEPA recently decided that synthetic pyrethroids and pyrethrins could be considered as a common mechanism group and could be assessed collectively through a cumulative risk assessment (USEPA 2011a).

The two different types of pyrethroid and the corresponding differences in the length of time the sodium channel is inactivated are associated with distinct syndromes in laboratory animals receiving high doses (USEPA 2011a). Type I pyrethroids are associated with the T-syndrome, characterised by aggression, hyperexcitability, fine tremor, prostration with coarse whole body tremor, increased body temperature, coma and death. Type II pyrethroids are associated with the CS-syndrome, characterised by choreoathetosis (whole body writhing) and salivation. Both syndromes are considered to be acute dose-dependent responses to pyrethroid exposure. Recovery is rapid in mammals (24-48 hours), due to the presence of extensive detoxifying enzyme systems, which are largely absent in insects.

While USEPA signalled that Type I and Type II pyrethroids may be considered as separate cumulative assessment groups (CAGs) in the future, in their most recent assessment all pyrethroids and pyrethrins were considered as a single CAG. USEPA determined that data from one unpublished and one published (Weiner et al 2009) study provided suitable consistent measures of pyrethroid toxicity (uniform measure of potency) to be used to determine relative potency of a range of pyrethroids and pyrethrins.

2.4.2 Observations in humans

Acute effects

Table 3 summarises the data for pyrethroid insecticide exposures reported by the AAPCC for the period 2001-2013. No pyrethroid exposures were reported prior to 2001. Reported pyrethroid exposures increased steadily from 2001 to 2012.

During the period 2001 to 2013, 18 fatalities due to pyrethroid exposure were reported. Details were provided for two of these fatalities; a 92 year old male, exposed via inhalation as the result of unintentional misuse, and a 40 year old male, exposed via inhalation and dermal contact following unintentional misuse. It should be noted that the specific pyrethroids involved in these incidents were not identified.

Table 3. Incidents of pyrethroid poisoning reported to US poison centres 2001-2013

Year[1]	Exposures reported		Age (years)					Reason				Treated in healthcare facility	Outcome[3]				
	Total	PYR	<6	6-12	13-19	>19	Unkn	Unint	Int	Other	Adv Rxn		None	Minor	Mod	Major	Death
2001	2267979	9751	3105		1158	5405		9091	241	51	351	1792	1669	2220	379	16	0
2002	2380038	12475	3915		1356	7067		11506	355	86	496	2260	2096	3010	537	25	0
2003	2395582	15171	4616		1638	8664		14070	361	97	611	2777	2367	3569	676	23	3
2004	2438644	18214	5310		1951	10760		16869	495	122	696	3094	2925	4308	747	30	0
2005	2424180	20022	5631		2134	12070		18599	528	126	731	3800	3005	4877	847	40	4
2006[2]	2403539	20526	5468		1801	9859		17941	418	142	633	3047	2977	4496	718	19	2
2007	2482041	21721	5857		2036	10452		19247	492	129	744	3317	3171	4999	669	20	0
2008	2491049	22620	5919		2199	11063		20057	506	140	734	3293	3508	5184	732	26	0
2009	2479355	23060	5768	1228	938	11770	2241	20356	575	165	795	3646	3395	5506	743	25	4
2010	2384825	24063	5897	1223	1013	12469	2254	21157	633	180	829	3612	3531	5735	773	12	2
2011	2334004	23979	5921	1321	1001	12277	2261	21168	601	164	774	3593	3742	5633	764	16	1
2012	2275141	25124	5836	1157	994	13172	2694	22157	692	167	761	3765	3719	6009	748	23	2
2013	2188013	23376	5484	1054	868	12284	2456	20502	599	198	780	3551	3541	5448	700	26	0

PYR = synthetic pyrethroid insecticides

Unkn = unknown

Unint = unintentional exposures, including passive environmental exposure, occupational exposure, therapeutic error or unintentional misuse

Int = intentional exposures, including suspected suicide and improper or incorrect use of a substance for a purpose other than its intended purpose

Adv Rxn = adverse reaction, an adverse event occurring with normal, prescribed, labelled, or recommended use of the product, as opposed to overdose, misuse, or abuse, including allergic, hypersensitive and idiosyncratic reactions

Mod = moderate

[1] Report references: (Bronstein et al 2007; Bronstein et al 2008; Bronstein et al 2009; 2010; Bronstein et al 2011; Bronstein et al 2012; Lai et al 2006; Litovitz et al 2001; Litovitz et al 2002; Mowry et al 2013; Mowry et al 2014; Watson et al 2003; Watson et al 2004; Watson et al 2005)

[2] From 2006 onwards there was a change in the way demographic information was reported; the 'PYR' exposure count represents all recorded exposures, but the counts in subsequent columns report single substance exposures only. Over all exposures, single substance exposures account for just over 90% of all exposures

[3] Minor = The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes.

Moderate = The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement

Major = The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement

A five-year review of pyrethrin and pyrethroid related illnesses in Washington and Oregon states (US) identified 407 cases that fitted the study definition (Walters et al 2009). There were 182 exposures to pyrethroids relevant to the current study (permethrin, tetramethrin, D-allethrin or phenothrin). It should be noted that the number of exposures is greater than the number of cases, as exposure was often to a mixture of active ingredients. Of these 182 exposures, only one was considered to be of high severity (permethrin).

An assessment of pyrethrin/pyrethroid-associated illness and injury was carried out for 11 US states for the period 2000-2008 (Hudson et al 2014). A total of 4974 cases were identified through a Sentinel Events Notification System. Table 4 provides a summary of details related to pyrethroids of interest to the current project.

Table 4. Surveillance of illness and injuries due to exposure to selected pyrethroids, 11 US states (2000-2008)

Active ingredient	Total cases	Low severity cases (%)[a]	Moderate or high severity cases (%)[a]	Respiratory symptoms (%)	Dermal symptoms (%)
Allethrin	27	23 (85)	4 (15)	8 (30)	10 (37)
Permethrin	350	283 (81)	67 (19)	137 (39)	141 (40)
Phenothrin	57	36 (63)	21 (37)	37 (65)	22 (39)
Tetramethrin	31	23 (74)	8 (26)	24 (77)	5 (16)

Source: (Hudson et al 2014)

[a] Cases were classified as low severity if three or fewer days of work were missed and the health effects were not likely to require treatment. Moderate severity related to health effects that are not life-threatening, but required medical treatment and resulted in time lost from work (usually less than 5 days). High severity refers to health effects that are life-threatening and require hospitalisation and usually more than 5 days off work.

Contributing factors to pyrethrin/pyrethroid exposure included spills or splashes (13%), off-target drift from the application site (12%), failure to evacuate the area during application (11%) and inadequate ventilation (10%). Fatalities involving the selected pyrethroids included:

- An 18-month child who drank an unknown amount of allethrin. The child developed cough, upper respiratory pain and irritation, nausea, vomiting, tachycardia and malaise before death.
- A 64-year-old woman who sprayed a permethrin/tetramethrin formulation above her head. Material from the can dripped down her arm and contaminated her clothing. The next morning she awoke with dyspnea and wheezing. The case was hospitalised for nine days with an asthma attack, respiratory depression, coma and cardiac arrest, resulting in death.

Chronic effects

Evidence for chronic adverse health effects due to exposure to low levels of pyrethroids has been reviewed (Kolaczinski and Curtis 2004). It was concluded that there was a general absence of well-designed studies to test this hypothesis. Studies that claimed to demonstrate adverse effects reported inconsistent symptoms resulting from pyrethroid exposure and could not rule out exposure to other pesticides.

A more recent review of epidemiological evidence for adverse human health effects due to pyrethroid exposure identified effects on sperm quality and sperm DNA, reproductive hormones, pregnancy outcomes and neurobehavioural development as potential toxicological endpoints (Saillenfait et al 2015). However, the authors of this review concluded that further studies were required to clarify the possible risks associated with long-term environmental exposure to pyrethroids.

It has been suggested that the presence of pyrethroids in the domestic environment could impact on the neurodevelopment of infants in those environments (Horton et al 2011). Children (*n* = 348) were assessed for cognitive and motor development at 36 months. Results were assessed in terms of the permethrin concentrations in maternal and umbilical cord plasma and in personal air samples, collected during pregnancy. No association was found between permethrin exposure and performance scores.

A Spanish study found that pesticide use in the home during pregnancy, but not during the post-natal period, was associated with a decrement in psychomotor development at 14 months (Llop et al 2013). However, the nature of the pesticides was not elaborated.

2.5 HEALTH EFFECTS – PIPERONYL BUTOXIDE

2.5.1 Regulatory assessments

Piperonyl butoxide (PBO) has been evaluated by JMPR and USEPA.

JMPR

PBO has been evaluated by JMPR in 1965, 1966, 1972, 1992 and 1995. The most recent evaluation was the most comprehensive (JMPR 1996). It was concluded that:

- PBO has negligible acute toxicity and is unlikely to present an acute hazard under normal conditions of use.
- PBO causes mild dermal and ocular irritation, but is not a skin sensitiser.
- Short- and long-term studies show that the liver is the main target organ. Toxicity is characterised by liver enlargement with associated hypertrophy of the hepatocytes, focal necrosis and alteration of some clinical chemical parameters (e.g. serum alkaline phosphatase activity).
- Following inhalation exposure (rat), effects were seen on the liver at the highest dose administered (512 mg/m^3 for 6 hours per day, 5 days per week). Irritation of the upper airway, presenting as squamous metaplasia of the larynx, was seen at all doses.
- PBO is not mutagenic or genotoxic, but has been shown to be carcinogenic (liver adenomas and carcinomas) at doses that cause general toxicity.
- PBO is not embryotoxic or teratogenic (rat, rabbit). Reduced pup weight and viability were seen in developmental toxicity studies in mice, but these effects appeared to be related to maternal toxicity.

An ADI of 0-0.2 mg/kg bw was established on the basis of an NOAEL of 16 mg/kg bw/day for liver toxicity in a one-year dog study, with application of a 100-fold safety factor.

USEPA

The USEPA assessment of PBO reached largely the same conclusions as the JMPR assessment, with chronic health assessment based on liver effects in dogs (USEPA 2006b). While no specific studies of neurotoxicity had been conducted, USEPA noted that "Neurotoxic effects of PBO are not evident from the clinical signs reported in developmental, reproductive, and chronic studies". USEPA did not find a common mechanism for PBO and any other substances.

2.5.2 Observations in humans

Little information was found on human toxicity of PBO. This is not surprising as humans will usually be exposed to PBO at the same time as exposure to pesticides, such as pyrethrins and pyrethroids.

While PBO is a potent inhibitor of the mixed function oxidase system in insects, antipyrine metabolism was not affected in human males (*n* = 9) after receiving a single dose of 50 mg PBO (Conney et al 1972).

The potential for pyrethroids and PBO in the domestic environment to impact on the neurodevelopment of infants in those environments was examined (Horton et al 2011). Children (*n* = 348) were assessed for cognitive and motor development at 36 months. Results were assessed in terms of the permethrin concentrations in maternal and umbilical cord plasma and permethrin and PBO in personal air samples during pregnancy. No association was found between permethrin exposure and performance scores. However, children with greater exposure to PBO (>4.34 ng/m^3 in 48 hour maternal personal air samples) scored significantly lower in terms of Mental Developmental Index (mean difference -3.9 points, 95th percentile confidence interval -0.25 to -7.49 points).

2.6 HEALTH EFFECTS - N-OCTYL BICYCLOHEPTENE DICARBOXIMIDE (MGK 264)

2.6.1 Regulatory assessments

JMPR

MGK 264 was assessed by JMPR in 1967, when it was concluded that "The toxicological data are inadequate to serve as a basis for an estimation of the acceptable daily intake for man" (JMPR 1967). There has been no subsequent update on this conclusion by JMPR.

USEPA

MGK 264 was reregistered by USEPA in 2006 (USEPA 2006a). USEPA assumed that MGK 264 did not have a common mechanism of toxicity with other substances. Consequently, a cumulative risk assessment was not required.

MGK 264 is of low acute dermal toxicity (LD_{50} > 2000 mg/kg bw) and is mildly irritant to skin and eyes. No suitable studies were available to assess acute oral and inhalation toxicity or skin sensitisation. The liver is the target organ for MGK 264 in subchronic and chronic toxicity studies.

MGK 264 was classified as a possible human carcinogen based on a significant increase in benign liver adenomas in mice, at doses approaching the limit dose. However, tumours occurred at doses higher than the NOAEL for systemic toxicity. MGK 264 did not exhibit reproductive or developmental toxicity. There was low concern of mutagenicity and genetic toxicity. There were no indications of immunotoxicity or neurotoxicity.

2.6.2 Observations in humans

No information was found on adverse health effects in humans from exposure to MGK 264.

3. DOSE-RESPONSE INFORMATION

3.1 AUTOMATIC INSECTICIDE DISPENSER FORMULATIONS

No dose-response information specific to automatic insecticide dispenser formulations was found.

3.2 PYRETHRIN/PYRETHROID INSECTICIDE FORMULATIONS

No dose-response information specific to pyrethrin/pyrethroid insecticide formulations was found.

3.3 PYRETHRINS AND PYRETHROIDS

USEPA have concluded that pyrethrins and pyrethroids (Type I and Type II) can be considered as a cumulative assessment group (CAG) for the purpose of risk assessment (USEPA 2011a).

Deltamethrin was selected as the index pyrethroid, due to availability of a good body of high quality toxicological data. A benchmark dose (BMD) associated with a 20% increase in neurobehavioural endpoints following a single acute dose was determined for deltamethrin. The BMD_{20} and the associated lower 95th percentile confidence limit ($BMDL_{20}$) were 14.5 and 10.5 mg/kg bw, respectively. For risk assessment, the $BMDL_{20}$ was rounded to 11 mg/kg bw.

Of the pyrethroids/pyrethrins present in automated insecticide dispenser formulations in New Zealand, tetramethrin and D-phenothrin (sumithrin) did not exhibit toxicity at doses of 5000 mg/kg in the reference studies and were considered to be substantially non-toxic to mammals. Oral relative potency factors (RPFs) for D-allethrin, permethrin and pyrethrins were 0.11, 0.09 and 0.02, respectively, relative to deltamethrin. Transfluthrin was not included in either of the reference studies. Transfluthrin is a Type I pyrethroid (no α-cyano group). Most of the Type I pyrethroids have RPFs substantially less than one. However, for the current study, a conservative position was taken and transfluthrin was assigned a RPF of 1 (equivalent in toxicity to deltamethrin). This appears to be a reasonable assumption, as the structurally similar pyrethroid, tefluthrin, has been shown to have a very similar threshold dose for effects on motor activity in rats to deltamethrin (Wolansky et al 2006).

Use of RPFs is based on an assumption of dose-additivity. USEPA concluded that available studies demonstrated good evidence of dose-additivity in the action of the pyrethroids and pyrethrins (Cao et al 2011; Wolansky et al 2006).

3.4 PIPERONYL BUTOXIDE

JMPR established an ADI of 0-0.2 mg/kg bw on the basis of an NOAEL of 16 mg/kg bw/day for liver toxicity in a one-year dog study, with application of a 100-fold safety factor (JMPR 1996). USEPA established a nearly identical chronic exposure limit (cPAD) of 0.16 mg/kg bw/day (USEPA 2006b). The only difference between these limits is that the JMPR value has been rounded.

USEPA also established an aPAD of 6.3 mg/kg bw/day for acute oral exposure. As there was no evidence of dermal toxicity, no exposure limits were derived. An acute inhalation NOAEL of 630 mg/kg bw/day was proposed. Assuming 100% absorption, this is the same as the oral point of departure. A short to long term inhalation LOAEL of 3.91 mg/kg bw/day was proposed, based on hyperplasia and metaplasia of the larynx in a subchronic rat study. It should be noted that there is evidence that metaplasia of the rat larynx may be an adaptive response, rather than a precursor to neoplastic changes (Osimitz et al 2007).

3.5 MGK 264

JMPR have not established an ADI for MGK 264 (JMPR 1967).

USEPA established an acute exposure limit (aPAD) of 1.0 mg/kg bw/day for dietary exposure by females aged 13-49 years of age (USEPA 2006a). No appropriate studies were available to derive an aPAD for other population groups. USEPA established a chronic exposure limit (cPAD) for all population groups of 0.061 mg/kg bw/day (LOAEL of 61 mg/kg bw/day, with a 1000-fold uncertainty factor). The same point of departure was applied to dermal exposure, with application of a 10% dermal absorption factor.

For inhalation exposure, the LOAEL of 0.01 mg/L (1.9 mg/kg bw/day) from a 90-day inhalation study in rats, for hyperplasia and metaplasia of the larynx, was defined as the point of departure. A 1000-fold uncertainty factor was again applied. It should be noted that there is evidence that metaplasia of the rat larynx may be an adaptive response, rather than a precursor to neoplastic changes (Osimitz et al 2007).

4. EXPOSURE ASSESSMENT

4.1 EXPOSURE SCENARIOS

Several studies have modelled exposure to pesticides or pesticide behaviour due to indoor release, either spraying or by evaporation (Berger-Preiss et al 2009; Bremmer et al 2006; Matoba et al 1993; Matoba et al 1995; Matoba et al 1998c; Vesin et al 2013). Exposure pathways relevant to the current assessment include:

- Exposure during installation of the insecticide reservoir (dermal and inhalation)
- Inhalation exposure by room occupants
- Dermal exposure by room occupants
- Dermal exposure to residues deposited on room surfaces (floor, furniture, etc.)
- Ingestion of insecticide following deposition on food or food contact surface or due to hand to mouth behaviour in young children

The first of these exposure routes is assumed to be relevant only to adults and will be infrequent, with material from manufacturers suggesting that a single reservoir refill should last for 4-15 weeks, depending on use parameters. For the remaining scenarios, the most sensitive group will be the very young (<1 year), due to their activity patterns (crawling on surfaces), their hand to mouth behaviour and their low body weight.

4.2 CONCENTRATION OF ACTIVE INGREDIENTS IN INSECTICIDE SPRAY

There are three active components present in automated insecticide dispenser formulations available in New Zealand, with different modes of action:

- Pyrethrin/pyrethroid insecticides (common mode of action)
- PBO
- MGK 264

4.2.1 Pyrethrin/pyrethroid insecticides

Based on the RPFs for pyrethrins/pyrethroids determined by USEPA in their cumulative risk assessment (USEPA 2011a), the insecticide component of all automated insecticide dispenser formulations can be converted to a common basis and expressed in terms of 'deltamethrin equivalents'. Table 5 lists the insecticide components of the various formulations available in New Zealand, the RPFs for the components and the composite insecticide concentration, expressed as deltamethrin equivalents.

Table 5. Conversion of insecticide formulation used in automatic insecticide dispensers to deltamethrin equivalents

Insecticide formulation (g/kg)	Active ingredient relative potency factor (RPF)	Insecticide formulation (g/kg deltamethrin equivalents)
Pyrethrins (9 g/kg)	0.02	0.18
D-allethrin (4.4 g/kg) Tetramethrin (3.5 g/kg) Pyrethrins (1.1 g/kg)	0.11 0.00 0.02	0.51
Tetramethrin (4.6 g/kg) D-phenothrin (0.83 g/kg) Permethrin (1.6 g/kg)	0.00 0.00 0.09	0.14
Transfluthrin (6.0 g/kg) Permethrin (8.0 g/kg)	1.00 0.09	6.72
Pyrethrins (9.75 g/kg)	0.02	0.20
Pyrethrins (9.25 g/kg)	0.02	0.19

Source: (USEPA 2011a)

Exposure assessments were carried out using the highest aggregate insecticide concentration of 6.72 g/kg deltamethrin equivalents. It should be noted that the formulation with the highest insecticide concentration, in terms of deltamethrin equivalents, does not include a synergist in the formulation.

4.2.2 Piperonyl butoxide

When PBO is used as a synergist, it is usually used at a concentration of 45 g/kg. One product reported a slightly lower PBO concentration (42.3 g/kg), while one product employed a mixture of PBO and MGK 264 as synergists and, consequently, contained a lower concentration of PBO (15.6 g/kg). A PBO concentration of 45 g/kg was used for exposure assessment.

4.2.3 MGK 264

Only one formulation contained MGK 264, as a mixed synergist with PBO. The concentration used (29.89 g/kg) was used for exposure assessment.

It should be noted that, although exposure assessments were carried out using these component concentrations, in reality this combination of concentrations would not occur. Specifically, exposure to the highest aggregate concentration of insecticides would be from formulations that do not contain synergists. Also, simultaneous exposure to both synergists can occur, but not at the PBO concentration chosen for this assessment.

4.3 INSECTICIDE SPRAYING PARAMETERS

Four parameters need to be considered in the spraying process:

- The volume of spray broadcast at each emission
- The frequency of emissions
- The proportion of the day over which emissions occur
- The proportion of the year over which emissions occur

The proportion of the year parameter is only relevant for chronic exposure assessment.

4.3.1 Spray volume

Most manufacturers of automatic insecticide dispensers or providers of refills for dispensers provide either direct or indirect estimates of the spray volume. Indirect evidence comes from the number of sprays expected from a specified weight of reservoir refill. Table 6 summarises spray volume information for providers operating in New Zealand.

Table 6. Spray volumes for automatic insecticide dispensers in New Zealand

Information provided	Spray volume (mg/spray)	Product/Source
A 185 g can will last 4 weeks or 6000 bursts	31	Raid
A 185 g can delivers 3000 metered sprays	62	Expra
A 520 ml can lasts up to 8 weeks or 10,800 bursts[a]	34	Ultrapel
Adjustable volume output (30 mg to 90 mg)	30-90	Ecomist
A 150 g can delivers 5000 metered sprays	30	Airomist
Metered dose is 25 mg per spray	25	Pyroshield
Metered Insecticide aerosol 150g contains 5000 activations	30	Py-Zapp

[a] Domestic insecticide sprays have specific gravity of about 0.7 g/mL

While most information suggests a normal spray volume of 25-35 mg, potential exists for spray volumes of up to 90 mg. The higher figure was used for the current assessment.

4.3.2 Spray frequency

Most of the automatic insecticide dispenser units available in New Zealand have adjustable spray frequencies. Table 7 summarises manufacturer information and standardises the information to 'sprays per hour of operation'.

Table 7. Spray frequency information for automatic insecticide dispensers available in New Zealand

Information provided	Spray frequency (sprays/hour of operation)	Product/Source
5 Mins - 30 Mins Spray Settings	2-12	Expra
Has an adjustable timer to spray every 5 or 7 minutes	8.6-12	Raid
Dispenser releases spray every 7 minutes	8.6	Ultrapel
Unit releases a ultra-fine mist into the atmosphere every 5, 10, 15 or 30 minutes	2-12	Pestrol
5 min to 18 min spray intervals	3.3-12	Airomist
Every 4, 7 or 15 minutes	4-15	Ecomist
Recommended setting of 15 minute spray intervals	4	Pyroshield

There is no evidence of a 'usual' spray frequency across different providers of automatic insecticide dispensers. A conservative approach was adopting in using the highest reported spray frequency (15 per hour) for exposure assessment.

4.3.3 Proportion of day automatic insecticide dispenser is operating

Automatic insecticide dispensers are capable of operating continuously and for the purpose of the current assessment it was assumed that dispenser would operate 24 hours per day.

4.3.4 Proportion of year automatic insecticide dispenser is operating

Insect control tends to be a seasonal activity in temperate climates. A five-month period, covering Summer, for domestic insecticide use was proposed in a Dutch model (Bremmer et al 2006), while a French study used a five-month annual use period for electric insecticide vaporisers (Vesin et al 2013). A five-month use period was used for the current assessment.

4.4 SPACE BEING TREATED

While some automatic insecticide dispensers are claimed to provide sufficient coverage for an entire house (150-170 m^2), the possibility must be considered that the spray from such units will be confined in a much more limited space. A Dutch model considered release of insecticides by electrical evaporators, a scenario that appears to be similar to the use of automated insecticide dispensers (Bremmer et al 2006). Electrical evaporators heat a solvent and active ingredient mix, resulting in volatilisation. Once in the colder air of the room, the solvent condenses and the active substance almost immediately and completely turns into droplets, which rise to the ceiling due to the warmer air.

The Dutch exposure model for electrical evaporators is based on installation in a small bedroom of 17 m^3 at 2.5 m ceiling height (room floor area of 7 m^2). However, a room area of 7 m^2 seem unlikely in New Zealand. Vesin *et al*. (2013) used a larger room size (32.3 m^3) for their exposure assessment for electrical evaporators. A New Zealand trade source reports the average size of a new single bedroom as 10.5 m^2 (26.3 m^3 for a ceiling height of 2.5 m)[4], although they also state that a single bedroom in an older house may be as small as 7.5 m^2. Automatic insecticide dispensers available in New Zealand do not appear to come with guidance on where they should be installed and it must be assumed that there is potential for them to be installed in small rooms with long occupancy periods such as bedrooms. For

[4] http://www.tradebox.co.nz/pb_resource.asp?resourceid=46 Accessed 14 October 2015

the current assessment a compromise single bedroom size (intermediate between an old and new single bedroom) of 22.5 m^3 was used.

4.5 DAILY EXPOSURE DURATION

The Dutch electrical evaporator model is based on installation of the evaporator in a small bedroom, resulting in a daily exposure duration of eight hours (Bremmer et al 2006). Additionally, it is assumed that a young child (10.5 months) will crawl over the floor of the bedroom for one hour per day. An eight hour exposure duration was also used in the study of Vesin *et al*. (2013). These parameters were used for the current assessment.

4.6 EXPOSURE MODELS

The ConsExpo model[5], developed by the Rijksinstituut voor Volksgezondheid en Milieu (RIVM; National Institute for Public Health and the Environment) in the Netherlands, is used by the European assessment of industrial chemicals (REACH) and biocides. Models for various exposure routes (inhalation, dermal or oral route) are included. The most appropriate exposure scenario and uptake model is chosen for each route. The parameters needed for the exposure scenario and the uptake models are then filled in. It is possible to choose for a screenings model or a higher tier exposure estimation.

The software model ConsExpo is a set of coherent, general models that enables the estimation and assessment of exposure to substances from consumer products that are used indoors and their uptake by humans.

ConsExpo includes several biocide application scenarios (Bremmer et al 2006). However, none of the models exactly match the situation of automated insecticide dispenser, that is, intermittent release of insecticide on an ongoing basis. The two potentially relevant models are:

- The air space application model. The model is based on a private user who sprays with an aerosol can in the living room to control flies or mosquitoes. Spraying is carried out from the middle of the room in the direction of the four upper corners.
- The electrical evaporator model. Electrical evaporators are used to kill insects, in particular flies and mosquitoes. An electrical evaporator is plugged into an electrical socket; the solvent and active substances are heated, resulting in evaporation.

The situation of an automated insecticide dispenser can be viewed as repetitions of the air space application model or as a non-continuous application of electrical evaporator model. The electrical evaporator model appeared most appropriate, as this model allows for increases in biocide concentrations in the air space. For this purpose, the insecticide release rate of 90 mg every 4 minutes was converted to a continuous release of 22.5 mg/minute.

Within the ConsExpo software, the basis for the calculation and/or estimation of the default parameter values is a ‘realistic worst-case scenario’. Scenarios consider consumers who frequently use a certain pest control product under less than favourable circumstances, such as relatively frequent use, application of a relatively large amount in a small room with a low ventilation rate, and a relatively long stay in that room.

The default parameter values in the models are chosen such that a relatively high exposure and uptake are calculated, in the order of magnitude of a 99th percentile of the distribution. To achieve this goal, the 75th or the 25th percentile is calculated (or estimated) for each

[5] http://www.rivm.nl/en/Topics/C/ConsExpo Accessed 15 October 2015

parameter. The 75th percentile is used for parameters which give a higher exposure for higher values, and the 25th percentile is used in the reverse case.

4.6.1 Inhalation exposure during dispenser operation

Inhalation exposure (internal dose) can be calculated from the equation:

$$\mathrm{E}_i = \frac{IR \times t \times C \times AF}{BW}$$

Where:

IR = inhalation rate (m^3/minute or hour)
t = exposure duration (minutes or hours)
C = concentration of substance of interest in inhaled air (mg/m^3)
AF = absorption factor
BW = body weight (kg)

The concentration of the substance of interest will be a function of the mass generation rate (spray rate), the spray duration, the room dimensions, the room ventilation rate, physicochemical characteristics of the spray and the proportion of the substance of interest in the spray formulation. These calculations are implicit in the ConsExpo model.

Inhalation exposure was estimated for an infant (1 year; 25th percentile body weight, average for male and female = 8.6 kg) sleeping 8 hours (480 minutes) in a room with an automated insecticide dispenser, set to dispense 90 mg every 4 minutes (22.5 mg/minute) of a formulation containing 6.72 g/kg deltamethrin equivalents, 45 g/kg PBO and 29.89 g/kg of MGK 264. Table 8 specifies the full range of parameters required by ConsExpo, the values chosen and rationale for choosing them.

Table 8. Parameters for inhalation exposure, electrical evaporator model of ConsExpo

Parameter	Value	Rationale
Spray duration	480 minutes	Continuous spraying for duration of exposure
Exposure duration	480 minutes	Sleeping period of 8 hours
Room volume	22.5 m^3	Area for New Zealand single bedroom, average of older and new, multiplied by standard room height
Room height	2.5 m	Standard room height
Ventilation rate	1/hr	Default model setting
Mass generation rate	22.5 mg/minute	Dispenser emitting 90 mg every 4 minutes
Airborne fraction	1 g/g	All insecticide formulation emitted enters the air
Weight fraction non-volatile	1 g/g	Vapour pressures (20-25ºC): pyrethrin I 6.9 x 10^{-5} Pa, pyrethrin II 2.7 x 10^{-5} Pa, D-allethrin 1.6 x 10^{-3} Pa, permethrin 7.0 x 10^{-5} Pa, D-phenothrin 1.6 x 10^{-4} Pa, tetramethrin 4.7 x 10^{-6} Pa, transfluthrin 9 x 10^{-4} Pa, PBO 1.3 x 10^{-5} Pa, MGK 264 2.4 x 10^{-3} (ConsExpo: <0.01 Pa = non-volatile)
Density non-volatile	1.0 g/cm^3	Density: pyrethrum 0.97-0.98, D-allethrin 1.0, permethrin 1.2-1.3, D-phenothrin 1.1, tetramethrin 1.1, transfluthrin 1.5, PBO 1.1, MGK 264 1.0
Initial particle distribution	Lognormal: median 8 μm (coefficient of variation 0.3)	From (Matoba et al 1994b)
Inhalation cut-off diameter	15 μm	ConsExpo default value
Uptake fraction (respirable proportion)	1	Assume 100% absorption
Inhalation rate	2.9 m^3/day	ConsExpo default for sleeping infant
Uptake fraction (non-respirable proportion)	1	Assume 100% absorption

Deltamethrin equivalents

Using the ConsExpo software, the scenario outlined above results in an inhalation exposure estimate of 0.013 mg/kg bw/day of deltamethrin equivalents, with an associated oral exposure, due to gastrointestinal clearance of non-respirable particles, of 2.9 x 10^{-5} mg/kg bw/day.

The ConsExpo software has a degree of opacity concerning the structure of the models used. To check the plausibility of the exposure estimate an oversimplified model was used to compare estimates. The oversimplified model assumed that the spray emission of 90 mg was uniformly distributed in the 22.5 m^3 bedroom space and that this concentration was maintain throughout the 8-hour sleeping period. In other words, a steady-state was achieved where spray settled out of the room volume at the same rate that it was added. An infant resting respiration rate of 0.003 m^3/minute (USEPA 2011b) was applied and it was assumed that all particles would be inhaled and absorbed. The oversimplified model results in an inhalation exposure estimate of 0.0045 mg/kg bw/day deltamethrin equivalents, suggesting that the estimate derived from ConsExpo is plausible.

Piperonyl butoxide

Using the ConsExpo software, the scenario outlined above results in an inhalation exposure estimate of 0.077 mg/kg bw/day of PBO, with an associated oral exposure, due to gastrointestinal clearance of non-respirable particles, of 1.7 x 10^{-4} mg/kg bw/day.

MGK 264

Using the ConsExpo software, the scenario outlined above results in an inhalation exposure estimate of 0.055 mg/kg bw/day of MGK 264, with an associated oral exposure, due to gastrointestinal clearance of non-respirable particles, of 1.2 x 10^{-4} mg/kg bw/day.

4.6.2 Inhalation exposure during reservoir installation

In most cases, correct installation of insecticide reservoirs will not result in any exposure to active ingredients. However, accidental activation of the spray mechanism is possible. ConsExpo adopts a scenario of contamination occurring within a 1 m^3 'personal space' of the person carrying out the task (Bremmer et al 2006). Mass generation rates for full spray cans have been reported to be in the range 0.53 to 2.15 g/second (Bremmer et al 2006). No objective data were available to parameterise this scenario, but if it is assumed that spray activation may occur for up to 2 seconds at the highest mass generation rate, with the installer (25th percentile body weight New Zealand adult, approximately 68 kg, inhalation rate for adult involved in light intensity activity of 0.012 m^3/minute) staying in the emission zone for about 1 minute, inhalation exposures of 0.005 mg/kg bw (deltamethrin equivalents), 0.03 mg/kg bw (PBO) and 0.02 mg/kg bw (MGK 264) can be estimated.

4.6.3 Dermal exposure

Three dermal exposure scenarios are relevant to automated insecticide dispensers:

- Spillage during loading of insecticide reservoirs
- Deposition on skin during operation
- 'Rub off' during contact with room surfaces

These scenarios are all lacking objective data from which to derive model parameters.

Dermal exposure from spillage during loading of insecticide dispensers

The ConsExpo model does not assess this particular scenario, but makes the following relevant points:

- Dermal contact with biocide activity ingredients during mixing and loading will usually be restricted to the hands
- ConsExpo has a default value for mixing and loading biocides of 0.01 mL, although other sources summarised in the ConsExpo fact sheet give exposure volumes up to 0.2 mL

Dermal absorption of the active ingredients present in automatic insecticide dispenser formulation is generally quite low. Estimates of dermal absorption of 1.2% for cypermethrin (Woollen et al 1992) and 0.35-0.52% for permethrin (Tomalik-Scharte et al 2005) have been reported from human volunteer studies. Studies on human skin, found 1.3 to 5.2% of applied doses of bifenthrin, deltamethrin and permethrin in the receptor fluid after 24 hours (Hughes and Edwards 2010). In a second experiment, including a skin wash, absorption did not exceed 2.2% after 48 hours. For participants in an exercise to examine dermal absorption from carpet, following pyrethrin application, dermal absorption was estimated to be 0.74%

Human volunteer studies demonstrated dermal absorption of PBO in the range 0.47 to 1.78% following an 8-hour non-occluded exposure (Selim et al 1999).

The USEPA assessment of MGK 264 reported dermal absorption of 10% MGK 264 (USEPA 2006a). However, it should be noted that in the volunteer study only 1% of the radiotracer was recovered from urine, while a further 9% was 'unaccounted for'.

It was conservatively assumed that 10% of the various components of automated insecticide dispenser formulation would be dermally absorbed.

Based on spillage of 0.2 mL (0.14 g at a density of 0.7 g/mL) of automatic insecticide dispenser formulation and 10% dermal absorption, for a 68 kg adult New Zealander, exposure to the three components of the formulation would be 0.0014, 0.0093 and 0.0062 mg/kg bw, for deltamethrin equivalents, PBO and MGK 264 respectively. It should be noted that exposure by this route is likely to be infrequent.

Dermal exposure from deposition on skin during operation

The primary risk assessment scenario relates to an infant sleeping for eight hours in a room with an automated insecticide dispenser in operation. In addition to inhalation exposure, some dermal exposure will occur due to skin exposed to deposited formulation during sleeping. For an infant, it seems reasonable to assume that it will be mainly the head region that is not covered by bedding or sleeping attire.

In addition to insecticide formulation being deposited on the floor, formulation will be absorbed onto the ceiling and walls, be lost from the room due to ventilation or will remain in the room air space. In a study of electrical evaporators, Matoba *et al*. (1994a) calculated that the amount of the pyrethroid on the floor and on the walls was comparable. They calculated that 12 hours after the start of the application, the amount of pyrethroid on the floor and on the walls was approximately 0.01% of the amount that was present on the ceiling, and was approximately 1% of the amount in the air.

In studies of 'fogging' of insecticides into a room of size 9.6 m^2, release of a total of 0.7 g of active ingredient resulted in average concentrations of the active ingredient (cypermethrin) on the floor of 4.2 $\mu g/cm^2$ (Keenan et al 2010). Fogging involves the complete release of the insecticide load in a short period of time (~40 seconds, in this case). Assuming that the amount deposited will be proportional to the amount emitted and that deposition at bed height will be similar to deposition at floor level, eight hours of operation of an automated insecticide dispenser, under the scenario outlined for the current study, would result in emission of 0.072 g deltamethrin equivalents, 0.49 g PBO and 0.32 g MGK 264.

The room size in the study of Keenan *et al*. (2010) was very similar (9.6 m^2) to that in the current scenario (9 m^2). Based on the similarity in room size and the assumption outlined above, active ingredient deposition in the current scenario would be 0.43 μg/cm^2 deltamethrin equivalents, 2.9 μg/cm^2 PBO and 1.9 μg/cm^2 MGK 264.

According to the USEPA exposure factors handbook, an infant (<1 year) head constitutes 18.2% of the body surface area (USEPA 2011b). The 75th percentile body surface area for an infant (6 to <12 months) is 0.48 m^2. As deposition can only occur on half of the head at any time, half the surface area of an infant head would be 0.044 m^2 or 440 cm^2.

Based on the deposition rates outlined above and assuming 10% dermal absorption for all compounds, this would result in exposure of 0.0022 mg/kg bw deltamethrin equivalents, 0.015 mg/kg bw PBO and 0.010 mg/kg bw MGK 264 for a 8.6 kg infant.

Dermal exposure from 'rub-off' during contact with room surfaces

For the 'rub-off' model, exposure (internal dose) is calculated from:

$$E_d = \frac{TR \times TC \times t \times AF}{BW}$$

Where:

TR = transferable residue (mg/cm^2)

TC = transfer coefficient, is area of contact between exposed skin and the residue containing media per unit time

t = contact time

AF = absorbed fraction

BW = body weight (kg)

The 'rub-off' model is based on an infant crawling on the floor, resulting in an area of skin-floor contract per unit time. The ConsExpo model uses a transfer coefficient for a crawling infant of 0.6 m^2/hour (Bremmer et al 2006). The ConsExpo model specifies a dislodgeable amount of 30%, that is, 30% of the active ingredient that deposits on the floor can be brushed off onto the skin surface. Based on one hour of crawling on an affected surface, the deposition rates outlined above, a 10% dermal absorbed fraction and 8.6 kg body weight, the resulting exposure to automatic insecticide dispenser formulation components would be 0.009 mg/kg bw/day deltamethrin equivalents, 0.06 mg/kg bw/day PBO and 0.04 mg/kg bw/day MGK 264.

4.6.4 Oral exposure

Oral exposure to residues of automatic insecticide dispenser formulation may occur due to:

- Infant hand-mouth behaviour during crawling contact with affected surfaces
- Contamination of food or plates used for serving food

In addition, inhaled particles over a certain size (cut-off diameter) are unable reach the lower regions of the respiratory tract and are deposited in the upper reach, from where they are cleared through the gastrointestinal system. The ConsExpo estimates oral exposure by this mechanism as part of the inhalation exposure model.

Oral exposure from infant hand-mouth behaviour

The ConsExpo oral exposure model for children is a corollary to the 'rub-off' model of dermal contact (Bremmer et al 2006). The hands are considered to account for 20% of the exposed skin surface and that 50% of the material on the hands is ingested due to hand-mouth behaviour. This means that oral exposure will be 10% of dermal exposure. However, dermal

absorption is set at 10%, while oral doses are generally assumed to be 100% absorbed. Consequently, the internal dose due to oral exposure will be the same as the internal dose due to 'rub-off' dermal exposure (see above).

Oral exposure from food consumption

To estimate potential exposure to automated insecticide dispenser formulation from consumption of food it was assumed that the active ingredients would end up on a dining plate at the floor deposition rates outlined in section 4.6.3. For an adult this was assumed to be a 30 cm diameter dinner plate (area 707 cm^2), while for an infant it was assumed to be a 20 cm diameter plate (area 314 cm^2). It was further assumed that all residues would transfer to food and be consumed. Assuming 100% absorption of all components and using the body weight previously specified for adults (68 kg) and children (8.6 kg), these equates to estimated oral exposure for deltamethrin equivalents, PBO and MGK 264, respectively of 0.0045, 0.030 and 0.020 mg/kg bw/day for adults and 0.016, 0.11 and 0.069 mg/kg bw/day for children.

It should be noted that these exposure estimates relate to a single contaminated meal per day. However, given that plates may be stored away from direct deposition or may be stacked, so that only the top plate receives direct deposition, assuming more than one fully contaminated meal per day seems unwarranted.

4.6.5 Summary of exposure estimates

Table 9 summarises the various estimates of exposure to automated insecticide dispenser formulation components for adults and children. All exposures are internal doses.

Table 9. Summary of estimated exposures to active ingredients in automated insecticide dispenser formulations

Scenario	Frequency	Estimated exposure (mg/kg bw/day)		
		Deltamethrin equivalents	**Piperonyl butoxide**	**MGK 264**
Child (<1 year)				
Inhalation (8 hours sleeping)	Daily	0.013	0.077	0.055
Dermal (8 hours sleeping)	Daily	0.0022	0.015	0.010
Dermal (1 hour crawling)	Daily	0.009	0.06	0.04
Oral (hand-mouth)	Daily	0.009	0.06	0.04
Oral ingestion (8 hours sleeping)	Daily	0.000029	0.00017	0.00012
Oral (contaminated food)	Daily	0.016	0.11	0.069
Total	**Daily**	**0.049**	**0.32**	**0.21**
Adult				
Inhalation (reservoir installation)	Occasional	0.005	0.03	0.02
Dermal (reservoir installation)	Occasional	0.0014	0.0093	0.0062
Total	**Occasional**	**0.006**	**0.039**	**0.026**
Oral (contaminated food)	Daily	0.0045	0.030	0.020

5. RISK CHARACTERISATION

The exposure scenarios selected for the current study mean that maximal risk will be assessed in terms of infant exposure. This is suitable from a risk assessment point of view, as it is the most conservative approach. However, it is uncertain whether the chosen scenario (installation of automatic insecticide dispenser in a small bedroom occupied by an infant) is likely to reflect actual practice.

All exposures have been calculated in terms of internal doses, assuming 100% absorption by the oral and inhalation routes and 10% absorption by the dermal route of exposure. It is assumed that all residues enter a common pool following absorption, allowing the various routes of exposure to be assessed in aggregate.

5.1 INFANT EXPOSURES

5.1.1 Pyrethrins/pyrethroids

There is limited evidence for chronic adverse health effects due to pyrethrin/pyrethroid exposure. Risks due to acute exposure (one day) were assessed in terms of margin of exposure (MoE), against the $BMDL_{20}$ of 11 mg/kg bw derived by USEPA in their cumulative risk assessment of pyrethrins and pyrethroids (USEPA 2011a). MOEs are calculated by dividing a defined point on the dose-response curve, such as the $BMDL_{20}$, by the estimates of exposure.

The MoE for aggregate infant exposure to pyrethrins/pyrethroids, expressed as deltamethrin equivalents, from use of automated insecticide dispensers is 11/0.049 = 224. USEPA derived a target MoE of 300 for children up to 6 years of age, including factors of 10 for inter-species and inter-individual variability and a factor of 3 to meet the requirements of the Food Quality Protection Act (FQPA), requiring a greater level of protection for the very young (USEPA 2011a).

The risk characterisation of the insecticidal component of the formulations is very strongly influenced by the assumption that the RPF for transfluthrin will be close to that of the reference compound, deltamethrin. The deltamethrin equivalents of non-transfluthrin-containing formulations in New Zealand are less than 10% of the transfluthrin-containing formulations (see Table 4). For these formulations the resultant MoEs would be greater than 2000 and of little concern. Similarly, most formulations available in New Zealand do not contain MGK 264 and the assessment of risks will only have relevance to people with brand loyalty to products containing MGK 264.

5.1.2 Piperonyl butoxide

Infant exposure to PBO was assessed by comparison of exposure estimates with the USEPA acute and chronic population adjusted dose (PAD) (USEPA 2006b). The acute PAD (aPAD) of 6.3 mg/kg bw for PBO provides a good margin between estimated daily aggregate exposure (0.32 mg/kg bw) and levels of exposure at which acute exposure would be a concern.

The estimated exposure exceeds the chronic PAD (cPAD) of 0.16 mg/kg bw/day. It should be noted that pest control is likely to be seasonal and information in the ConsExpo fact sheet suggests that insect pest control is usually in operation for 3-6 months of the year, with a figure of 5 months proposed for domestic pest control (Bremmer et al 2006). On this basis the daily exposure estimated in the current study would equate to a chronic dose of 0.15 mg/kg bw/day, just within the cPAD.

5.1.3 MGK 264

Infant exposure to MGK 264 was assessed by comparison with the USEPA acute and chronic population adjusted dose (PAD) (USEPA 2006a). The acute PAD (aPAD) of 1.0 mg/kg bw for MGK 264 provides a good margin between estimated exposure (0.21 mg/kg bw) and levels of exposure at which acute exposure would be a concern. However, it should be noted that this aPAD is only applicable for 19-49 year old women and no suitable data were available to derive acute exposure limits for other population subgroups.

The estimated exposure exceeds the chronic PAD (cPAD) of 0.061 mg/kg bw/day. It should be noted that pest control is likely to be seasonal and information in the ConsExpo fact sheet suggests that insect pest control is usually in operation for 3-6 months of the year, with a figure of 5 months proposed for domestic pest control (Bremmer et al 2006). On this basis the daily exposure estimated in the current study would equate to a chronic dose of 0.088 mg/kg bw/day (143% of the cPAD).

5.2 ADULT EXPOSURES

Adult exposures were mainly assessed to examine risks that may result from accidental activation of automated insecticide dispenser reservoirs during installation. As this occurrence will be infrequent (less than once per week and generally less than once per month), the estimated exposures were assessed as acute events.

For pyrethrins/pyrethroids, the MoE between the $BMDL_{20}$ (11 mg/kg bw) and the estimated exposure during reservoir installation (0.006 mg/kg bw) of approximately 1800 exceeds the USEPA target MoE for adults of 100 (USEPA 2011a).

Exposure to PBO (0.039 mg/kg bw) is well below the USEPA aPAD of 6.3 mg/kg bw (USEPA 2006b), while estimated aggregate exposure to MGK 264 (0.026 mg/kg bw) is well below the USEPA aPAD of 1.0 mg/kg bw (USEPA 2006a). However, it should be noted that the MGK 264 aPAD is only defined for adult females.

5.3 GENERAL COMMENTS

Three-quarters of estimated infant exposure to the chemicals of interest is due to exposure calculations depending on the rate of deposition of formulation residues on the floor or near-floor levels (dermal exposure during operation, dermal exposure during crawling, hand-mouth oral exposure and contaminated food oral exposure). Rates of deposition used were in the range 0.43 to 2.9 $\mu g/cm^2$, depending on the component considered. Studies of actual pesticide residues on residential floors have found maximum concentrations of pyrethroids in the $\mu g/\mathbf{m^2}$ range (Lu et al 2013; Obendorf et al 2006; Trunnelle et al 2014); approximately one-thousandth of the rates used in the current study. However, there is no evidence that these studies included residences where automatic insecticide dispensers were being used.

In contrast, studies of the period following broadcast spraying of a room with an insecticide formulation containing 5 g/kg active ingredient found concentrations on the floor of approximately 10^5 $\mu g/m^2$ active ingredient (10 $\mu g/cm^2$) (Matoba et al 1995). Experimental observations were consistent with a mathematical model developed by the same group. In a further study by the same group measured floor residues after applying a formulation containing pyrethroids (tetramethrin and D-phenothrin) for 2.5 minutes, four times over an 8-week period (Matoba et al 1998a). The total amount of formulation released over the 8-week period was 250 g. The model used in the current study would equate to release of approximately 1800 g of formulation over eight weeks of continuous operation. Matoba *et al*. (1998b) measured concentrations of the two pyrethroids on the floor during the spraying period of 2200 and 2500 $\mu g/m^2$ (0.22 and 0.25 $\mu g/cm^2$). In a further study, a pyrethroid-containing formulation (tetramethrin and resmethrin) was sprayed in a room for two periods of 10 seconds each day for 30 days (Matoba et al 1998b). Total formulation used was 270 g,

compared to approximately 970 g under the scenario used in the current study. Concentrations of tetramethrin and resmethrin measured on the floor were 6810 and 173 $\mu g/m^2$ (0.68 and 0.017 $\mu g/cm^2$), respectively. These studies suggest that the active ingredient deposition rates used in the current study are not unreasonable.

An experimental study measured concentrations of PBO and two pyrethroids (tetramethrin and permethrin) at floor level 20 minutes after a 2-second spray (Zoubiri 2011). Concentrations were in the range 0.08 to 0.24 $\mu g/cm^2$. After seven days, concentrations had decreased by about 30%.

6. CONCLUSIONS

Insecticidal formulations used in automatic insecticide dispensers usually contain two main components of toxicological concern; an insecticidal agent and a synergist. Synergists inhibit the mixed function oxidase enzymes that detoxify the insecticidal agent. The insecticidal agents used in automatic insecticide dispensers in New Zealand are pyrethrins and/or synthetic pyrethroids. The pyrethroids used are mainly Type I or older Type II pyrethroids and are mostly of low toxicity. The synergists used are either PBO or MGK 264.

There is good evidence for acute adverse health effects in humans associated with exposure to the insecticidal chemicals present in automatic insecticide dispensers (pyrethrins/pyrethroids), but limited evidence of adverse health effects from operation of automatic insecticide dispensers, or from chronic low dose exposures. There is little evidence of adverse health effects in humans from exposure to synergists. However, humans will rarely be exposed to these chemicals in isolation from insecticidal agents.

Due to the diversity of insecticidal active ingredients used in these products, risk assessment of pyrethrins/pyrethroids was carried out using a cumulative risk assessment approach, as these insecticides are considered to exert their toxicity by a common mode of action (USEPA 2011a), specifically interaction with voltage-gated sodium channels in nerve tissues. Relative potency factors were available for all relevant insecticides, except transfluthrin. It was assumed that the potency of transfluthrin was equivalent to that of the reference pyrethroid (deltamethrin). There is no evidence that the synergists used in these products can be considered as a common mechanism group and this assessment has considered exposure to automatic insecticide dispenser formulations in terms of three separate components; pyrethrins/pyrethroids as deltamethrin equivalents, PBO and MGK 264.

Exposures were considered in terms of a realistic worst-case scenario; installation of the automatic insecticide dispenser in the bedroom of an infant (<1 year). The dispenser was assumed to operate 24 hours per day. Daily exposure was assessed as the aggregate of; inhalation during eight hours of sleeping, dermal exposure during eight hours of sleeping (assuming exposure of the head only) and during one hour of crawling (contact with insecticide formulation deposited on the floor) and oral exposure due to non-respirable particles being ingested during sleep and deposition of insecticide formulation on food. It was assumed that only one meal per day would be affected and that deposition on food was the same as deposition on the floor of the bedroom. Adult exposure potentially associated with insecticide formulation reservoir installation was also considered, assuming an accidental two second activation of the dispenser. Exposures were aggregated over all identified exposure routes. Absorption of all compounds was assumed to be 100% following inhalation or oral exposure and 10% following dermal exposure.

Risks associated with aggregate pyrethrin/pyrethroid cumulative exposures were assessed by MoE, while aggregate exposures for PBO and MGK 264 were assessed against acute and chronic PADs.

Infant pyrethrin/pyrethroid aggregate cumulative exposure were at a MoE of 224, less than the target MoE of 300, proposed by USEPA for this age group (USEPA 2011a). Acute aggregate exposures to PBO and MGK 264 were less than the respective aPADs. However, chronic aggregate exposures to PBO and MGK 264 approached or, in the case of MGK 264, exceeded respective cPADs. It should be noted that MGK 264 is only present in one formulation identified on the New Zealand market; the market share of that formulation is unknown.

Adult exposures to automatic insecticide dispenser formulation during reservoir installation are unlikely to result in acute adverse health effects.

While most assumptions made in this exposure assessment will tend to overestimate exposure to components of automatic insecticide dispenser formulation, these results suggest that use of such dispensers under the conditions of this scenario may lead to undesirably high exposure to some of the component chemicals. The two largest components of the aggregate exposure estimates are to infants from inhalation during sleep and consumption of contaminated food. This suggests that these dispensers are probably best installed in living spaces, rather than in bedrooms or food preparation areas.

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